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Netherlands Cancer Institute), Plesmanlaan 121, NL-1066 CX Amsterdam (NL).

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(72) Inventors; and

(75) Inventors/Applicants (for US only): **VELDMAN, Robert, Jan** [NL/NL]; Lis 18, NL-1273 CD Huizen (NL). **VAN BLITTERSWIJK, Wim, J.** [NL/NL]; Burg. Vijl-briefstraat 24, NL-1551 TK Westzaan (NL). **VERHELJ, Marcel** [NL/NL]; Von Bonninghausenlaan 38, NL-2161 ET Lisse (NL). **KONING, Gerben, A.** [NL/NL]; Stro-camp 23, NL-3992 BR Houten (NL).

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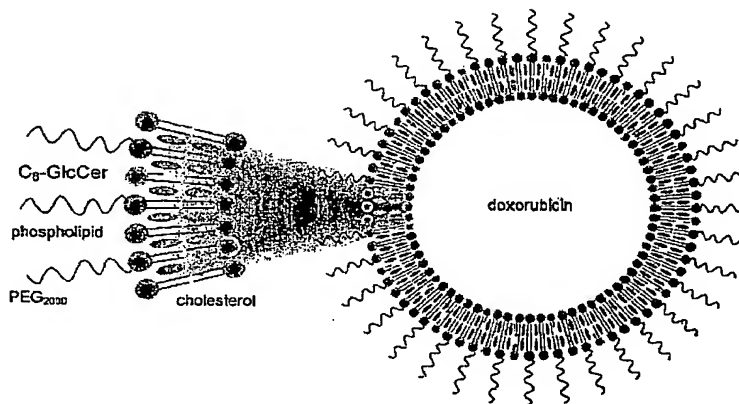
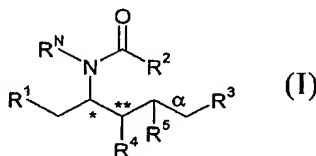
(74) Agents: **WYTENBURG, Wilhelmus et al.**; Mewburn El-lis LLP, York House, 23 Kingsway, London Greater Lon-don WC2B 6HP (GB).

(71) Applicant (for all designated States except US): **HET NEDERLANDS KANKER INSTITUUT** [NL/NL]; (The

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(54) Title: PHARMACEUTICAL FORMULATIONS EMPLOYING SHORT-CHAIN SPHINGOLIPIDS AND THEIR USE



(57) Abstract: This invention pertains to pharmaceutical formulations which comprise (i) a drug (e.g., an amphiphilic drug) (e.g., an anthracycline) (e.g., doxorubicin) and (ii) a short-chain sphingolipid (e.g., a short-chain glycosphingolipid or a short-chain sphingomyelin) (e.g., N-octanoyl-glucosylceramide, referred to as C₈-GlcCer) (e.g., N-hexanoyl-sphingomyelin, referred to herein as C₆-SM), and which provide improved drug delivery and efficacy. The short-chain sphingolipids selected from compounds of the following formula (I), wherein R¹ is independently: an O-linked saccharide group; or an O-linked polyhydric alcohol group; or: R¹ is independently: an O-linked (optionally N-(C₁₋₄alkyl)-substituted amino)-C₁₋₆alkyl-phosphate group; or an O-linked (polyhydric alcohol-substituted)C₁₋₆alkyl-phosphate group; R² is independently C₃₋₉alkyl, and is independently unsubstituted or substituted; R³ is independently C₇₋₁₉alkyl, and is independently unsubstituted or substituted; R⁴

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

is independently -H, -OH, or -O-C₁₋₄alkyl; R^N is independently -H or C₁₋₄alkyl; the bond marked with an alpha (α) is independently a single bond or a double bond; if the bond marked with an alpha (α) is a double bond, then R^S is -H; if the bond marked with an alpha (α) is a single bond, then R^S is -H or -OH; the carbon atom marked (*) is independently in an R-configuration or an S-configuration; the carbon atom marked (**) is independently in an R-configuration or an S-configuration; and pharmaceutically acceptable salts, solvates, esters, ethers, chemically protected forms thereof. In one embodiment, the pharmaceutical formulation is a liposomal pharmaceutical formulation prepared using a mixture of lipids comprising, at least, vesicle-forming lipids (e.g., phospholipids) (e.g., phosphatidylcholines) (e.g., fully hydrogenated soy phosphatidylcholine (HSPC)) (e.g., dipalmitoyl-phosphatidylcholine (DPPC)) and said short-chain sphingolipid, and optionally cholesterol and optionally a vesicle-forming lipid which is derivatized with a polymer chain (e.g., a phosphatidylethanolamine (PE) which is derivatized with polyethyleneglycol (PEG)) (e.g., N-(carbonyl-methoxy-polyethylene glycol 2000)-1,2-distearoyl-sn-glycero-3-phosphoethanolamine sodium salt (MPEG2000-DSPE)). The present invention also pertains to methods for the preparation and use of such formulations.